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Helms Award Lecture

Interplay Between Pediatric Pharmacy Practice and Research to Influence Patient Care

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I am honored and grateful to be chosen as the 2009 Richard Helms Award recipient. This recognition has a special meaning since it carries the name of an individual who has contributed so much to pediatric pharmacy through innovative practice, education and research, especially in the area of parenteral nutrition, as well as mentoring numerous outstanding students, residents, fellows and colleagues over the years. This award is also particularly meaningful because I am able to share this recognition with many of my former fellows and students who are here today. Furthermore, this recognition is an honor because it is coming from the Pediatric Pharmacy Advocacy Group (PPAG) and its members who are dedicated to the improvement of the lives of pediatric patients.

It has been a privilege for me to be actively involved in pediatric pharmacy practice, teaching, research and service activities over the past 30 years. I discovered the rewards of patient care, teaching and research during my education and training, and thus pursued an academic position which could combine all of these functions. In 1977, Ohio State University recruited the first group of fulltime clinical faculty and Children's Hospital in Columbus offered basic pharmacy services to patients. As the first clinical pharmacist at Children's, my goal was to develop a pediatric pharmacy practice and research program to improve health care. My objective today is to share how these activities have interconnected to influence patient care.

Soon after I began my practice in pediatric infectious diseases, numerous patients were admitted with Reye's syndrome. They required high dose glycerol therapy to control the intracranial pressure. Our interdisciplinary team was able to lower morbidity and mortality by adjusting doses to maintain certain serum concentration of glycerol in patients.[1] This finding was instrumental in establishing the value of collaboration among the disciplines of medicine, pharmacy and nursing at the hospital.

Bacterial meningitis was a frequently encountered infection during the pre-Hib vaccine era, and chloramphenicol was the drug of choice for empiric treatment since the third-generation cephalosporins were not available. Chloramphenicol serum concentrations were routinely monitored to prevent dose-related hematologic toxicities. Similarly aminoglycoside (gentmicin or tobramycin) therapy was being monitored by measuring peak and trough serum concentrations to ensure efficacy and minimize adverse effects. During routine monitoring we found that serum concentrations were unpredictable, sometimes trough concentrations being similar to or exceeding the peak concentrations. This led to designing a series of studies to evaluate the effect of drug infusion rate and injection site on serum concentrations. The results were crucial to influence changes in infusion sets and pumps,

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and in developing intravenous drug administration guidelines to assure complete delivery of intended doses to patients.[2-4]

The pharmacokinetic studies with chloramphenicol showed marked variability; we also found that infants had higher bioavailability than children due to decreased renal clearance of its prodrug chloramphenicol succinate; accumulation of the prodrug led to higher amount of the active drug, chloramphenicol.[5,6] Aminoglycoside and vancomycin pharmacokinetics studies demonstrated that the dose requirements depended on patient demographic factors including gestational and postnatal age, and birth weight.[7-11]

We had a number of patients with short bowel syndrome and it was not clear if drugs could be given by oral or rectal route effectively among these patients. Our studies in a piglet model showed that certain drugs were well absorbed throughout the small and large intestine.[12,13]

We conducted the first pharmacokinetic studies with azithromycin in children with acute otitis media, which led to the development of dosage guidelines in this population.[14] In adult patients with cystic fibrosis, we showed aminoglycosides may be used effectively and safely with once daily regimen.[15]

We performed population pharmacokinetic studies with amlodipine in children and adolescents with hypertension.[16] Pharmacokinetic and pharmacodynamic studies were also done with a number of additional drugs including antimicrobials, analgesics, anticonvulsants, antiinflammatory drugs and bronchodilators. We were also able to perform a number of efficacy and safety studies with antimicrobials, analgesics, antihypertensives, antiinflammatory agents and sedatives. These studies identified dosage requirement for various drugs such as ondansetron in cancer patients,[17] amlodipine in patients with hypertension,[18] etanercept in rheumatoid arthritis,[19] and oral hypoglycemic agents in type 2 diabetes.[20]

In the early 1980s, meperidine, promethazine and chlorpromazine were the most commonly used drugs, which were administered as a cocktail, for procedural sedation. The clinical observation of prolonged sedation and respiratory depression in some patients led us to study this cocktail further. We found a clear association between its use and prolonged sedation as well as respiratory depression.[21] We conducted additional studies with benzodiazepines and meperidine, which led to routine use of these drugs and discontinuation of the cocktail.[22-24]

We were curious about the relationship between drug class and associated adverse effects. Antibiotics, opioids, anticonvulsants and antireoplastic agents were most frequently associated with adverse effects.[25] Importantly, most adverse events could be prevented at the time a medication is ordered, administered and during the monitoring stages.[25] Conversely, only a few could be prevented at the medication dispensing or transcribing stages.[25]

Health services research allows us to perform pharmacoepidemiologic studies. In a cross sectional study of 18.6 million visits over a 10–year period, we found that 80% of patients with sleep difficulties received a prescription medication and yet none of these agents have received FDA approval.[26] Off label use of drugs is common in children. As a member of an Institute of Medicine committee, I was asked to present a lecture on medication use in children and a question arose about the off label use of drugs in the emergency department. In a study of nearly 7000 medication orders written for 2200 patients, we found 26% of the orders were for off label use. The adverse drug reactions, however, occurred in less than 1% of patients, not different from the frequency observed for drugs with FDA approval.[27]

In the early phase of my career, it became clear that many drugs were not available in appropriate formulations for use in infants and young children. Many intravenous drugs were too concentrated to measure small doses accurately, and tablets or capsules could not be used in younger patients unable to swallow them. This situation provided an opportunity to utilize my background in pharmaceutics to conduct the stability, compatibility and sterility testing. Our book *Pediatric Drug Formulations,* now in fifth edition, lists extemporaneous formulations for commonly used drugs including our studies.[28]

The diversity of research projects (e.g., pharmacokinetics/pharmacodynamics, drug delivery, efficacy/safety, extemporaneous formulations and health services studies) has been interesting and has allowed us to focus on the most clinically relevant questions that needed answered for patient care. It also provided an opportunity to match our research needs with funding opportunities. The research findings have led to

improved dosage regimens to achieve desired health outcomes.

Teaching has been strengthened due to research. I have brought research data to the classroom which has stimulated student interest in pursuing pediatric practice or research. Over 40 postdoctoral fellows or graduate students and 100 pharmacy students have made significant contributions to our research program and the care of pediatric patients. Active involvement in professional and scientific organizations has also been fruitful in learning from colleagues by enhancing my practice, research and teaching performance.

In summary I believe good research questions emanate from practice, and addressing these questions through research improves patient care. In fact, an interplay between practice, research, teaching and service can lead to an exciting career. It is important to remember that the center of all theses activities are people, whether they are patients and caregivers, students, or fellows and colleagues.

I have learned that pursuing a passion with positive thinking and persistence, enjoying the work, learning continuously, building collaborative relationships, and being a team player can lead to a productive and satisfying career. I have been very fortunate to have had so many opportunities in practice, teaching, research and service, and to have attracted superb trainees and collaborators to work with me. I am deeply indebted to the fellows and students, patients and caregivers, colleagues, collaborators and mentors, and friends and family for their work and support. Thanks to all of you for honoring me today and for your contributions to pediatric pharmacy.

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